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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,276	03/02/2001	Jai Wook Park	05823.0193	7049

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Finnegan Henderson Farabow
Garrett & Dunner
1300 I Street NW
Washington, DC 20005-3315

EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

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DATE MAILED: 05/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/786,276

Applicant(s)

PARK ET AL.

Examiner

Zachary C. Tucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-9 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 does not meet the requirements of 35 U.S.C. 112, second paragraph, for the following reasons:

- The structures for the ruthenium complexes (1), (2) and (3) are partially handwritten. Some of the structures of (2) and (3) is illegible. It is suggested that applicant re-draw these structures without handwriting in order to insure that all of the structural variables therein are clearly set forth.
- Claim 1 is presented in a manner so as to create uncertainty as to whether or not the claimed process ends at the step, "...an acyl donor compound to supply acyl group [sic] to said lipase," because the period, which should conclude the claim, appears only after the structural formulae for the reactants and products involved in the process. Claim 1 does not complete the sentence "What is claimed is..." and instead ends with a dangling phrase consisting of a series of structural formulae and definitions for variables in the formulae. In order to remedy this deficiency,

the structural formulae should be set forth after each recitation of the element said structural formulae represent in the claimed process, with a period after the last step in the claimed process.

- The identity of the acyl donor, required in the process of claim 1, is undefined. Claim 1 has been examined as though the "acyl donor" is *p*-chlorophenyl acetate or isopropenyl acetate, since these are the only examples of an acyl donor suggested in the specification. Because the only acyl group taught in the broad disclosure is acetyl, the only possible identity of R³ in the product chiral ester is methyl (making the compound of formula (100) an acetyl ester).
- The substituents on R¹, R² and R³ are set forth as "heteroatoms," with one example, a halogen atom, given. The phrase "such as" does not render the claim indefinite, rather, the lack of a distinct group of possible heteroatoms in the claim renders the claim indefinite. Additionally, supposing that the heteroatom(s) might be an atom other than a halogen atom, such as a silicon atom, a situation wherein there are dangling valencies on the heteroatom(s) is created, which renders claim 1 further indefinite. Claim 1 has been examined as though the optional substituents on R¹; R² are defined as halogen, cyano, or methoxy.
- In the definition of the variables R¹, R² and R³, a cyano group is characterized as a heteroatom. A cyano group is a functional group,

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made up of two atoms, and is therefore not a heteroatom. Characterizing a cyano group as an atom is repugnant to its definition.

- In the definition of the variables R^1 , R^2 and R^3 , it is specified that R^1 and R^3 and/or R^2 and R^3 can be cyclized each other (cyclized *with* each other is grammatically correct). Given the steps in the process, a chiral ester of the formula (100) wherein R^1 and R^3 and/or R^2 and R^3 are cyclized with each other is not possible, as this product would be formed by an *intramolecular* esterification reaction. The chiral alcohol and the acyl donor cannot be one in the same, according to the process as claimed.

Claim 2 does not meet the requirements of 35 U.S.C. 112, second paragraph, because the racemic alcohol of the formula (4b) lacks an antecedent basis in claim 1. The optional substituents on R^1 and R^2 are set forth in claim 1 as individual atoms (*i.e.*, "a hetero atom"). A methoxy group is not an atom. Claim 2 depends from an indefinite base claim, and is also indefinite for this reason.

Claim 3 depends from an indefinite base claim, and thus is indefinite.

Claim 4 depends from an indefinite base claim, and is further indefinite for the recitation, "...wherein X is Cl, Br or I, *the most preferably Cl.*" Bearing in mind that written description is where the preferred embodiments are to be set forth, claim language wherein one embodiment is specified as being preferred over another embodiment is at best superfluous. The claims are what applicant is seeking the right to exclude others from practicing, making, etc. A statement in the claims to the effect that one embodiment of the invention is preferred over another implies that applicant

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would not prefer patent protection for the "non-preferred" embodiments. The recitation in claim 4 that "X" is preferably Cl renders claim 4 ambiguous. Claim 4 has been examined as though this qualifying statement were not present therein.

Claims 5-8 depend from an indefinite base claim, and thus are indefinite.

Claim 9 depends from an indefinite base claim, and thus is indefinite. Claim 9 is further indefinite for the following reasons:

- There is no antecedent basis in claim 7, from which claim 9 depends, for the "said aryl ester" specified in claim 9.
- "alkenyl acetate" is characterized in claim 9 as an aryl ester. An alkenyl acetate is a *type* of compound, not a distinct chemical compound, and furthermore is not an aryl ester.

Claim 9 has not been further examined on the merits because the spirit of claim 9 is embodied in claim 1. The broad disclosure of the invention given in the specification makes clear that only two acyl donors are contemplated in the claimed process, *p*-chlorophenyl acetate and isopropenyl acetate. Claim 1 was examined with these two acyl donors in mind, as the identity of the acyl donor is not defined in claim 1, which required the examiner to look to the specification for the meaning of the term "an acyl donor."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Persson et al, *J. Am. Chem. Soc.* vol. 121, pages 1645-1650 (13 February 1999) in view of Koh et al, *Tetrahedron Letters*, vol. 39, pages 5545-5548 (1998) and further in view of Mahmoudian et al, *Biotechnol. Appl. Biochem.*, vol. 29, pages 229-233 (1999).

The process of claims 1-9 would have been obvious to one of ordinary skill in the art at the time the invention was made, given the teachings of Persson et al, Koh et al, and Mahmoudian et al.

Persson et al discloses a dynamic kinetic resolution process wherein a racemic alcohol of the formula (4) in instant claim 1 is converted to an enantiopure chiral alcohol in the presence of a ruthenium complex and *C. Antarctica* lipase.

Persson et al discloses two ruthenium complexes as racemization catalysts, one of which is, like the ruthenium complex of the formula (1) in instant claim 1, a triphenylphosphine-liganded ruthenium complex (page 1646, complex "1"). Persson et al states that this complex provides for faster racemization, but teaches that its use is not feasible in the dynamic kinetic resolution process in combination with a lipase due to the requirement for inorganic hydroxide when this complex is employed, which interferes with the enzyme. The complex exemplified by Persson et al in a dynamic kinetic resolution process is the complex designated as "2" in that reference, which is not a complex according to instant claim 1. Persson et al, as stated in the preceding sentences, characterizes the complex "2" as having decreased racemization activity when compared with "1." The deficiency of Persson et al with respect to the process of

claims 1-9 is that a different ruthenium complex is employed in the process disclosed therein.

The Koh et al reference explores the racemization activity of another ruthenium complex, which is a ruthenium complex of the formula (1) in instant claim 1 (page 5545). The ruthenium complex disclosed in the Koh et al reference is highly active in the racemization of chiral alcohols of the formula (4), as specified in claim 1. This complex requires the presence of a base for activity. Koh et al expressly suggest incorporating this ruthenium complex into a dynamic kinetic resolution (page 5545).

Koh et al exemplifies racemizations wherein potassium hydroxide, potassium *t*-butoxide, potassium carbonate, sodium hydride and triethylamine are the bases employed with the ruthenium complex of formula (1) (Table 1, page 5546).

Koh et al teaches away from the use of an alkoxide as the base in a dynamic kinetic resolution wherein the ruthenium complex is coupled with a lipase, because the alkoxides react with the acyl donors necessary for such a dynamic kinetic resolution (page 5548).

One of ordinary skill, motivated by the desire to avail himself of the superior racemization activity of the complex studied in the Koh et al reference, would have to select either sodium hydride, potassium carbonate or triethylamine as the base he would employ in the ruthenium complex – lipase system.

To one of ordinary skill in the art, that triethylamine is the appropriate base to select from this group is at once obvious. Sodium hydride is a strong reducing agent which reacts vigorously with lower alcohols (The Merck Index, 13th ed. pp.1541-1542),

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which are a necessary component of the reaction milieu in the dynamic kinetic resolution of a racemic secondary alcohol. Sodium hydride, would also be expected to react chemically with the acetyl esters employed as acyl donors in Persson et al's dynamic kinetic resolution. Potassium carbonate is a strong base, like potassium *t*-butoxide and inorganic hydroxides, and would interfere with the enzyme's activity.

Koh et al, though the observation that DBU, potassium carbonate, and triethylamine are much less effective than KOH or NaH when employed with racemization catalysts studied in that reference, does not teach that these less-effective bases are totally inactive.

Triethylamine increases the activity of *C. Antarctica* lipase. Mahmoudian et al, *Biotechnol. Appl. Biochem.*, vol. 29, pages 229-233 (1999), teaches that the addition of triethylamine to the reaction mixture wherein *C. Antarctica* lipase is employed in the acetylation of the drug "506U78" increased reaction rates and decreased the formation of side products (page 231).

Thus, one of ordinary skill in the art would select triethylamine as the basic reagent employed in combination with the ruthenium complex of the formula **1a**, as disclosed in the Koh et al reference, in a dynamic kinetic resolution with the *C. Antarctica* lipase, despite Koh et al's observation that it is much less effective than potassium hydroxide.

One of ordinary skill, motivated a desire to harness the superior racemization activity of the ruthenium complex disclosed in the Koh et al reference in the dynamic

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kinetic resolution scheme disclosed in the Persson et al reference, and guided by the teachings in the cited prior art, would have arrived at the claimed invention.

Cited of Interest

The following is pertinent to applicant's disclosure, published before the filing date of KR 1999/45040, and authored by the same group as the inventive entity in the instant case:

Koh et al, "Enzymatic resolution of secondary alcohols coupled with ruthenium-catalyzed racemization without hydrogen mediator" Tetrahedron Letters, vol. 40, pages 6281-6284 (20 August 1999).

The process of claims 1-9 is disclosed in this publication.

Specification

The specification is objected to because the abstract of the disclosure is more than one page long. An abstract may be no more than 25 lines or 250 words.

Correction is required. See MPEP § 608.01(b).

There are several spelling errors in the specification. It is suggested that applicant proofread the specification and correct obvious errors. For example "summary" is spelled "summery" on page 2, line 15 and "isopropenyl acetate" is spelled "isoprophenyl acetate" on page 8, line 18. In the examples, "reddish" is misspelled as "redish."

Conclusion

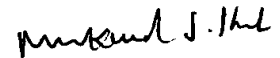
Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (703) 305-2050. The examiner can normally be reached Monday-Friday from 7:00am to 3:30pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (703) 308-4716. The fax number for the organization where this application or proceeding is

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assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

zt

A handwritten signature in black ink, appearing to be 'Z. L. M.' or similar, written in a cursive style.A handwritten signature in black ink, appearing to be 'Mukund Shah', written in a cursive style.

Mukund Shah
Supervisory Patent Examiner
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